Comparison of azathioprine and beta interferon efficacy on measures of inflammatory activity and brain damage evaluated by MRI in relapsing-remitting multiple sclerosis.

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Background

In relapsing remitting multiple sclerosis (RRMS) patients azathioprine (AZA) is at least as effective as beta interferons (IFN) on clinical and MRI outcome me (Massacesi et al 2014). In the present study efficacy of the two drugs on brain MRI measures of inflammatory activity and parenchimal damage was further explored.

Aim of the study

To compare efficacy of AZA and IFN on MRI measures of neuroinflammation and brain damage in a population of RRMS patients prospectively followed for two-years.

Methods

- Patient inclusion criteria:
  - Diagnosis of RRMS; age 18-55; at least two clinical relapses in the two previous years; EDSS 1-5.5.
  - included in the preselected Centers of the MAIN Trial, partecipating to the MRI ev**aluation.**
- The patients were randomized to AZA or IFN at inclusion and followed for two years.
- MRI scans were performed at baseline (T0), month 12 (T12) and month 24 (T24)

Endpoints

Primary :

New FLAIR lesions number and volume at the T0-T24 interval.

Secondary

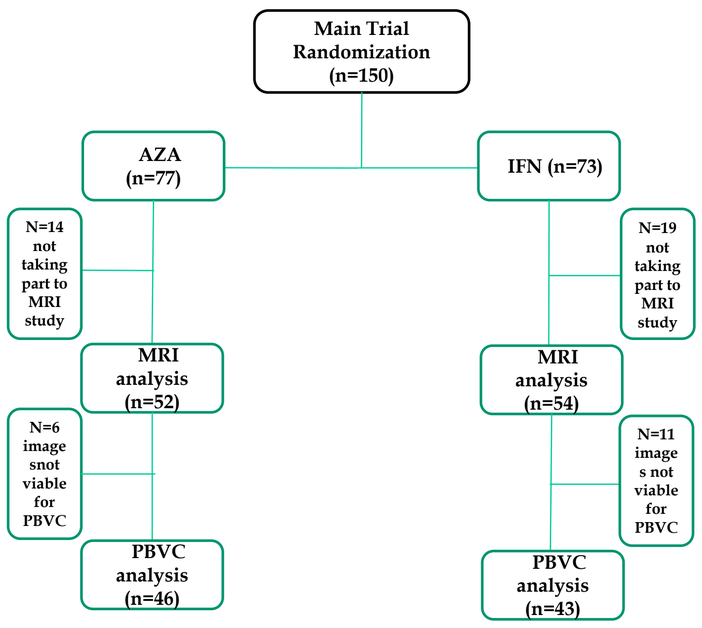
New FLAIR lesions number and volume at the T0-T12 and T12-T24 intervals.

Gd enhancing lesions number at month 12 and month 24

T1 hypointense lesions number T0-T24

Percentage Brain Volume Change (PBVC) at the T0-T24 interval (SIENA)

Patients participating to the MRI evaluation



Baseline clinical and demographic characteristics 1

	Randomized by treatment		Total
	AZA	IFN	
Totale (%)	52 (49,1%)	54 (50,9%)	106
Females (%)	35 (67,3%)	38 (70,4%)	73 (68,9%)
	p=0.73		
Age Mean (+ SE) Median	39±1.26 39	37± 1.25 37	38± 0.9 38
	p=0.17		
Disease duration Mean (+SE) Median	6,9±1,02 3,2	5,2±0,72 3,3	6,1±0,62 3,3
	p=0.47		
Baseline EDSS Mean (+SE) Median	1,9±0,1 1,5	1,9±0,13 1,5	1,9±0,08 1,5
	p=0.69		
Relapses from onset Mean (+SE) Median	4,3±0,43 3	3,8±0,23 3	4,0±0,24 3
	p=0.97		
Relapses, two prev. years Mean (+SE) Median	2,4±0,12 2	2,4±0,09 2	2,4±0,07 2

Baseline clinical and demographic characteristics comparison with MAIN trial

	MRI study		MAIN Trial	
	AZA (N=52)	IFN (N=54)	AZA (N=77)	IFN (N=73)
F (%)	35 (67,3%)	38 (70,4%)	49 (63,6%)	50 (68,5%)
Age	39±9,1	37±9,2	38,1±8,9	36,6±8,8
Disease duration	6,9±7,3	5,2±5,3	6,8±7,1	5,7±5,7
Baseline EDSS	1,9±0,8	1,9±1,0	1,9±0,9	1,9±0,9
Relapses previous 2 years	2,4±0,9	2,4±0,7	2,4±0,8	2,4±0,9

- No differences between the MRI study and the MAIN Ttial population
- No differences between the MRI study sample and the PBVC subgroup

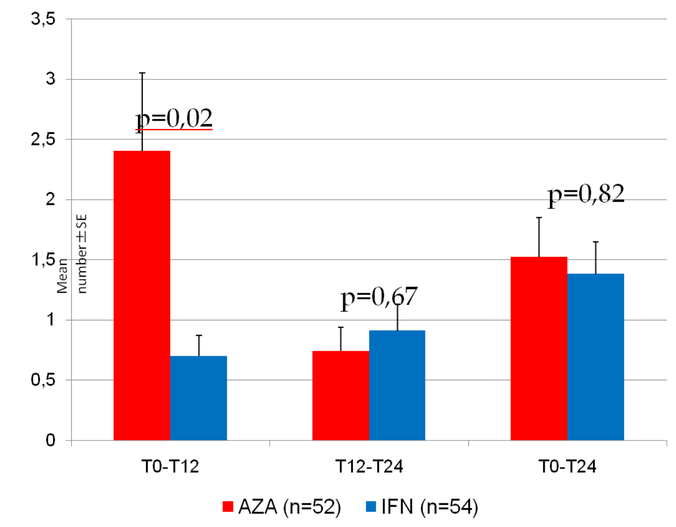
MRI study population clinical course

	Randomized patients	
	AZA	IFN
Annualized Relapse Rate		
Mean (+ SE)	0,31±0,06	0,40±0,07
Median	0	0
	p=0.67	
EDSS change		
Mean (+ SE)	-0,10±0,13	0,12±0,13
Median	0	0
	p=0.95	
Time to first relapse		
Mean (+ SE)	521±38,87	498±40,74
Median	727	694
	p=0.74	

MRI outcome measures

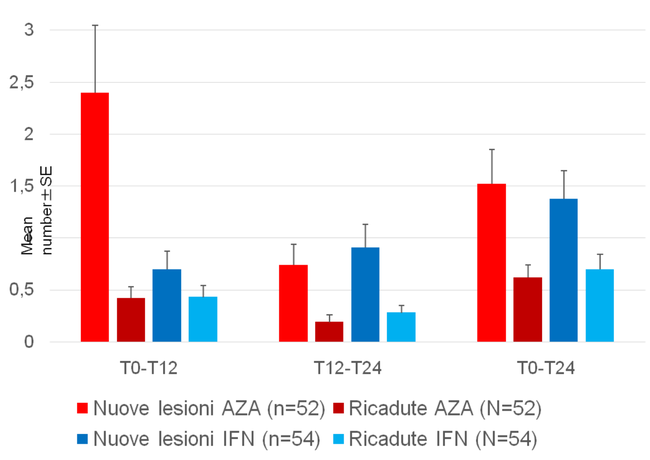
	New FLAIR lesion numbe r T0-T24	New FLAIR lesion volume T0-T24	New FLAIR lesion numb er T0-T12	New FLAIR lesion numbe r T12-T24	Gd+ lesion number T12	Gd+ lesion numb er T24	Black holes T0-T24	PBVC T0-T24	
AZA									
Mean SE Medi an	1,52 0,33 0	257 84,88 170	2,4 0,65 1	0,74 0,2 0	0,5 0,23 0	0,2 0,07 0	2,2 4,05 0	-0,5% 0,18 -0,38%	
IFN									
Mean SE Medi an	1,38 0,27 1	306 107,8 8 55	0,7 0,17 0	0,91 0,22 0	0,17 0,09 0	0,4 0,18 0	1,6 3,1 0	-1,06% 0,19 -0,97%	
p	0,82	0,66	0,02	0,67	0,3	0,68	0,33	0,02	

New FLAIR lesions number

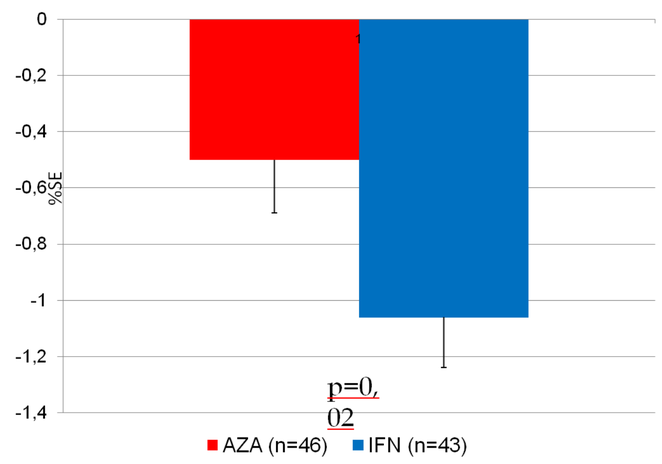


Disease activity

new FLAIR lesion number and clinical relapses



Percentage Brain Volume Change T0-T24



Discussion

Measures of disease activity:

- no differences on efficacy on the MRI outcomes over the whole observation period
- New brain lesion number was greater in the AZA arm at the T0-T12 interval, but not at the T12-T24 nor T0-T24 intervals.
- Vanishing lesions in the AZA arm in 13/52 patients (25%)
- The greater number of new brain lesions observed in the AZA arm during the first year was not associated with a greter number of clinical relapses

Vanishing Lesions

- Present in the AZA group only
- Lesion volume did not differ from persisting lesions
- Vanishment not related to oedema reabsorption

- Hypothesys

Qualitatively different because of differences in kynetics/action mechanism between two drugs

IFN activity in the fitst year suppresses BBB damage associated to «benign» lesions with a no impact on clinical status and natural history

Measures of CNS damage

- Brain atrophy over 2 years was lower in the AZA arm.
- Noteworthy, the difference was significant with a relatively small sample, indicating relevance of the difference
- Atrophy rates observed in the IFN arm are consistent with the present data (*Filippi 2004, Barkhof 2014*).
- Effect size of AZA on PBVC similar to that previously observed for second line therapies (Barkhof 2014)
- These data raise the hypothesis that AZA is very effective in preventing brain atrophy due to MS, though the undelying mechanism remains to be established

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